

composition sodium chloride and potassium phosphate,
respectively.

REMARKS

In order to respond to the rejection of the originally presented claims under 35 USC 112, 102 and 103, the originally presented claims have been canceled and replaced by newly presented Claims 20-27 which more particularly point out the subject matter that Applicants regard as the invention and contain no formal defects. No new matter has been added.

The currently presented claims are placed in "Jepson" format and are directed to compositions for replenishing electrolytes lost by passive transpiration/perspiration. The present invention is based on the discovery that the electrolyte loss due to passive transpiration/perspiration is different from the electrolyte loss from strenuous physical exertion. Compositions used to replenish electrolyte levels lowered by strenuous physical exertion may be unsuitable and, in some situations, harmful in replenishing electrolyte levels lowered by passive transpiration/perspiration. The presently claimed invention is directed to an improvement in compositions for replenishing electrolytes lowered by passive transpiration/perspiration and is clearly patentably distinct from the prior art cited by the Examiner.

The Stray-Gundersen reference, hereinafter referred to as US '723, discloses hypotonic beverage compositions for orally administering electrolytes and other ingredients to a human body. This reference also discloses that general activity, as well as various illnesses and operations, can cause hypohydration. However, this reference does not recognize that different electrolytes need different levels of replenishment depending on how the electrolyte levels were lowered or disclose all of the claimed components. Therefore, the secondary references must provide these teachings.

The Paul et al reference, hereinafter referred to as US '538, discloses a sustained energy composition for combating the consequences of strenuous physical exercise, trauma,

malnutrition, etc., which comprises a blend of a wide variety of ingredients. This reference, like US '723, has no disclosure regarding the differences between electrolyte loss due to strenuous physical exertion and electrolyte loss due to passive transpiration/perspiration. Therefore, this reference in combination with US '723 cannot possibly teach electrolyte supplements for replenishing electrolyte losses due to passive transpiration/perspiration. As such, the presently claimed invention is clearly patentable over the combination of US '723 with US '538.

EP 387 042, hereinafter referred to as EP '042, discloses the use of Rutin as an antioxidant, nutritive element, stabilizer in various drinks, foods, beverages, etc. and as a preventative and remedy for diseases. However, like US '723 and US '538, EP '042 has no recognition of the different electrolyte replenishment requirements depending on whether the electrolyte loss was due to strenuous physical exertion or passive transpiration/perspiration. Since the present invention is directed to an improvement in compositions for replenishing electrolytes lost by passive transpiration/perspiration, it is clearly patentably distinguishable over US '723 in combination with US '538 and EP '042.

Since the currently presented claims are placed in "Jepson" format and the preamble constitutes a limitation, the prior art cited by the Examiner should be directed to compositions for replenishing electrolytes lost by passive transpiration/perspiration in order to make a proper showing of prima facie obviousness under 35 USC 103. However, only the primary US '723 reference even speaks to hypohydration caused by nonstrenuous exertion and even then, this reference has no recognition of the different electrolyte replenishment needed for electrolyte loss caused by this phenomena. The remaining references have no recognition at all between strenuous physical activity electrolyte depletion and passive transpiration/perspiration electrolyte depletion. As such, the combination of references cited by the Examiner clearly do

not make a showing of prima facie obviousness with respect to the claimed invention.

Reconsideration of the present application and the passing of it to issue is respectfully solicited.

Respectfully submitted,


for Terryence F. Chapman

TFC/smd

FLYNN, THIEL, BOUTELL	Dale H. Thiel	Reg. No. 24 323
& TANIS, P.C.	David G. Boutell	Reg. No. 25 072
2026 Rambling Road	Ronald J. Tanis	Reg. No. 22 724
Kalamazoo, MI 49008-1699	Terryence F. Chapman	Reg. No. 32 549
Phone: (269) 381-1156	Mark L. Maki	Reg. No. 36 589
Fax: (269) 381-5465	David S. Goldenberg	Reg. No. 31 257
	Sidney B. Williams, Jr.	Reg. No. 24 949
	Liane L. Churney	Reg. No. 40 694
	Brian R. Tumm	Reg. No. 36 328
	Tricia R. Cobb	Reg. No. 44 621

Encl: Marked-Up Amended Specification and Abstract
Substitute Abstract
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IN THE SPECIFICATION

Please amend the specification as follows.

Please replace the paragraph beginning on page 1, line 21, and ending on page 1, line 32, with the following rewritten paragraph.

It has been~~will~~ established that along with eccrine transpiration, significant amounts of electrolytes are eliminated, which may account for systemic losses of up to 75 mEq of Na⁺ and Cl⁻, 60 mEq of K⁺ and Ca⁺⁺, and 10 mEq of HCO₃⁻ (Seutter et al., *The Quantitative Analysis of Some Constituents of Crude Sweat*, *Dermatologica* 141:226-233, 1970; Cage et al., *Eccrine Glands in Dermatology in General Medicine*, Fitzpatrick et al., McGraw-Hill, pp. 691-704, 1987). That such electrolyte losses may have negative consequences for the normal function of the human body has since long been recognized. The electrolyte losses consequent to excessive sweating, for instance in athletes, may contribute to early exhaustion, fatigue, muscle cramps, cardiac effects (arrhythmias) and CNS effects (asthenia). For this reason rational compositions have been successfully developed to reintegrate electrolyte losses by means of suitable rehydration beverages.

Please replace the paragraph beginning on page 6, line 3, and ending on page 6, line 14, with the following rewritten paragraph.

Apart from this obvious preoccupation on the carbohydrate component, the Inventors surmised that there could be significant physiological differences between the

rehydration needs of young sportsmen and those of middle-aged and elderly people passively undergoing therapeutic heat application. It had indeed been reported by Fukumoto et al. in *Differences in Composition of Sweat Induced by Thermal Exposure and by Running Exercise*, Clinical Cardiology 11:707-709, (1988) that the composition of sweat differed significantly between volunteers when engaged in strenuous physical activity, and the same volunteers when submitted passively to environmental heat. They reported that during the passive heat conditions much lower amounts of sodium and chloride ions were found in the collected sweat samples than in the physical exercise conditions, whereas the levels of potassium ions were found to be comparable in both conditions.

Please replace the paragraphs beginning on page 10, line 1, and ending on page 10, line 28, with the following rewritten paragraphs.

None of these subjects suffered renal, cardiac, nervous or metabolic disorders (in particular diabetes was excluded). These patients underwent the standard treatment protocol, consisting of once daily hot mud applications for 10 subsequent days. The mud used in~~was~~ a natural clay mixture biologically activated by means of a ripening process based on several months' exposure to running hot spring water at temperatures between 50°C and 80°C. The applied mud packs have an initial average temperature of around 50°C. The mud is applied on the trunk and on the affected part if distal, after which the subject is wrapped in several layers of cotton sheet for at least 30 minutes, during which profuse sweating will

typically appear. From all subjects sweat samples were collected, by means of polythene cups applied to the side of the forehead, for at least 10 minutes during the central part of the treatment session. Typically between 1 and 5 ml of transpiration fluid was collected from each subject.

A further series of 19 subjects (average age 40.3 years, range 32 to 52) did not undergo mud baths, but submitted to outside swimming and sunbathing in the same establishments where the thermal therapy was administered. Sweat samples were collected similarly from these subjects after a morning of leisure sunbathing at the hottest time of the day.

Analyses of the single sweat samples were performed as described by Fukumoto et al. (cited hereinabove) and by Hohnadel et al., *Atomic Absorption Spectrometry of Nickel, Copper Zinc, and Lead in Sweat Collected from Healthy Subjects During Sauna Bathing*, *Clinical Chemistry* 19(11): 1288-1292, (1973).

Though lacking an experimental group which engaged in physical exercise, a typical profile for passive heat-induced sweat emerged from experimental data, as will be summarized as follows:

Please replace the paragraph beginning on page 13, line 16, and ending on page 13, line 22, with the following rewritten paragraph.

In the case of sodium, the essential issue lies in the time/volume rate of sweat production. Indeed, sweat is

formed in two steps: production by the secretion coils of primary fluid containing nearly isotonic, NaCl concentrations, followed by reabsorption of NaCl in the duct. Ductal reabsorption efficiency being critically influenced by transit time, it is the sweat rate which is the most important factor influencing final NaCl concentration in sweat. Indeed, sweat NaCl is low at the low sweat rate range, increasing to isotonicity with increasing sweat rate.

Please replace the paragraph beginning on page 14, line 26, and ending on page 15, line 3, with the following rewritten paragraph.

Considering the observations on the risk of early skin ageing on repeated exposure to heat, especially if in conjunction with sun or UV exposure, it was further considered appropriate to include, besides a dermatropic element such as zinc, also a significant presence of the main dermoprotective vitamins such as biotin and beta-carotene. Since the main mechanism for cutaneous tissue damage on UV exposure is free radical induction and consequent peroxidation of skin surface lipids, and also considering that the principal hydro-soluble antioxidant ascorbic acid had previously been implicated in heat adaption mechanisms (Strydom et al. *in Effect of ascorbic acid on rate of heat acclimatization*, J. Appl. Physiol. 41(2): 202-205, 1976), a significant presence of vitamin C appeared desirable.

Please replace the paragraph beginning on page 15, line 15, and ending on page 15, line 30, with the following rewritten paragraph.

As a preferred alternative, the hydro--soluble glycoside of a natural antioxidant flavonoid, Rutin (quercetin-3-rutinoside) can be included in the composition of the present invention. On intestinal absorption, Rutin is readily metabolized to yield the polyphenol quercetin. The latter compound has recently been reported to be an extremely active free radical trapper, particularly active in protecting Low Density Lipoproteins (LDL) from oxidative damage (deWhalley et al., *Flavonoids Inhibit the Oxidative Modifications of Low Density Lipoproteins by Macrophages* Biochemical Pharmacology 39(11): 1743-1750 1989; Negre-Salvayre and Salvayre, *Quercetin Prevents the Cytotoxicity of Oxidized LDL on Lymphoid Cell Lines*. Free Radical Biology and Medicine 12 101-106 1992; Frankel et al. in *Inhibition of oxidation of human low-density lipoprotein by phenolic substances in red wine*, The Lancet 341: 454-457 1993). Rutin has indeed been reported to potentiate the synergistic antioxidant properties of the two main antioxidant vitamins (C and E) by Negre-Salvayre et al. in *Additional antilipoperoxidant activities of alpha-tocopherol and ascorbic acid on membrane-like system are potentiated by rutin*, Pharmacology 42(S): 262-272, 1991.

Please replace the paragraph beginning on page 16, line 24, and ending on page 16, line 26, with the following rewritten paragraph.

On the basis of the above general formula, the following specific compositions, prepared as a beverage, powder for dispersion in water, or solid forms for oral intake, such as capsules or tablets, are presented:

Please replace the paragraph beginning on page 18, line 20, and ending on page 18, line 27, with the following rewritten paragraph.

The above powder mix ~~is additional~~ can be combined with a suitable support for tablet compression, with good organoleptic properties, such as sorbitol and magnesium stearate. The mass is possibly edulcorated with a known natural sweetener such as xylitol and the total energy content should not exceed 20 kcal in the average daily intake. The product may be flavored with any choice of fruit or other flavors, such as orange, lemon, menthol, eucaplytol, or the like. The compressed tablets (or equivalent solid forms with the same composition) are intended for an average daily intake of between 5 and 10 tablets.

Please replace the paragraph beginning on page 21, line 12, and ending on page 21, line 19, with the following rewritten paragraph.

HOT CLIMATES - In today's modern society the technology of air conditioning has largely reduced the problem of the well known negative influence on human body function of high environmental temperatures. But a consistent chain of conditioned air cannot always be maintained, and a certain level of exposure to outside temperatures is often unavoidable. Less affluent and slower developing economies in geographical areas with hot climates will frequently be expoded to high temperatures, with all the negative effects, for instance when walking outside or traveling.

Please replace the paragraphs beginning on page 22, line 27, and ending on page 23, line 17, with the following rewritten paragraphs.

FEVER - When you run a fever, the body temperature control mechanism is upset due to the presence of an infection or other disturbing factors. The body temperature increases, not due to externally applied heat, but due to internal biological factors. The profuse sweating that is often associated with fever, especially in children, is well known. From a medical point of view a primary objective is the elimination of the infection (by prescribing antibiotics), and checking the fever (by prescribing antipyretics). An additional factor, mostly viewed as being less important from a medical point of view, is the re-establishment of an appropriate electrolyte balance, in the cases where profuse sweating has caused risk of excess electrolyte excretion. It is deemed that sweating due to endogenous heat is similar to sweating induced passively by external heat.

As a matter of fact, it is well known that sports beverages are often prescribed for this purpose. The present invention, while not being a medical treatment of the fever, may better assist to re-establish the balance of electrolytes upset due to sweating induced by endogenous heat.

Apart from the uses specifically discussed above, several other beneficial uses of the invention may be devised. Though the invention was not developed for sports

purposes and is not intended to balance electrolyte losses due to heavy physical activity, there are situations of moderate exercise where beneficial effects have been suggested, for example:

IN THE ABSTRACT

Please amend the abstract as follows.

COMPOSITION FOR THE RELIEF OF HEAT STRESS

ABSTRACT OF THE DISCLOSURE

A composition for the relief of heat stress, particularly for restoration of electrolyte balance due to passive exposure to heat resulting in excessive transpiration/perspiration, without strenuous physical activity, ~~comprises~~contains predetermined levels of selected electrolytes including, in part by weight, sodium ion not exceeding 250 parts, at least 100 parts of potassium ion, at least 100 parts of magnesium ion, and carbohydrates not exceeding 2.5% by weight, as needed for organoleptic purposes only. The composition can further include up to 30 parts of zinc, up to 10 parts of manganese, and from 65 to 400 parts of calcium. Furthermore, the composition can ~~comprise~~contain oligoelements, dermoprotective vitamins and anti-oxidants so as to compensate for the chemical changes which might occur in the skin of a person passively exposed to heat.